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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,277	12/04/2003	Gary J. Rosenthal	42830-10010	7142

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EXAMINER	
ROBERTS, LEZAH	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
09/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/728,277	ROSENTHAL ET AL.	
	Examiner	Art Unit	
	Lezah W. Roberts	1614	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,15,17,19,20,24,25,31,35,38,133-137,140,142,143 and 145-152* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,15,17,19,20,24,25,31,35,38,133-137,140,142,143 and 145-152* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §.119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *A-B*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the amendment filed July 5, 2007. All previous rejections have been withdrawn unless stated below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action mailed March 23, 2006.

Information Disclosure Statement

The information disclosure statement filed December 22, 2006 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Claims

Claim Rejections - 35 USC § 103 – Obviousness (New Rejections)

1) Claims 1, 15, 17, 19-20, 24-25, 31, 38, 133-137, 140, 142-143 and 145-152 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoeck et al. (US 6,620,428) in view of Krezanoski (US 4,188,373).

Hoeck et al. disclose compositions for delivering N-acetyl cysteine transdermally. The reference discloses that it may be beneficial to deliver the N-acetyl cysteine using a transmucosal method along with the disclosed transdermal method in order to enable the drug to reach the system more rapidly when needed (col. 12, lines 1-34). The reference differs from the instant claims insofar as it does not disclose the transmucosal delivery compositions comprise poloxamer 407.

Krezanoski discloses pharmaceutical delivery vehicles comprising polyoxyethylene-polyoxypropylene to deliver active agents to the mucous membrane. The polyoxyethylene-polyoxypropylene pharmaceutical vehicles of this invention have been unexpectedly found to increase drug absorption by the mucous membrane. Moreover, it has also been found that the pharmacologic response is unexpectedly prolonged. Drug action is typically both increased and prolonged by a factor of 2 or more. At the same time, protection is afforded to the involved tissues. A preferred polyoxyethylene-polyoxypropylene block copolymer for use in the pharmaceutical vehicle of this invention is one in which the number of polyoxyethylene units is about 70% of the total number of monomeric units in the molecule, as recited in claims 138-139. "Pluronic F-127" is such a material (col. 5, lines 23-61). The pharmaceutical compositions comprise from about 10% to about 26%, preferably from about 17% to about 26% of the copolymer and from about 74% to about 90% by weight water, the vehicle having a sol-gel or gel transition temperature in the range of from about 25°C to about 40°C, preferably from about 25°C to about 35°C, and especially from about 29°C to about 31°C (col. 3, lines 1-19), which encompasses claim 137. It may be concluded

that a range from 2 to 8°C the compositions will be a liquid. The compositions may also comprise components such as glycerin (Example 2). The compositions also include preservatives. In regards to the viscosity, the vehicles of the reference uses overlapping amounts of poloxamer, 10 to 20%, and water, as the compositions of the instant claims. That being said, the compositions of the reference should have the substantially the same viscosity profile as those of the instant claims. The reference differs from the instant claims insofar as it does not disclose the pharmaceutical agent is a N-acetyl cysteine.

It would have been obvious to one of ordinary skill in the art to have delivered the compositions poloxamers to deliver the N-acetyl cysteine of the primary reference motivated by the desire to increase drug absorption by the mucous membrane for rapid introduction into the system, as disclosed by the secondary reference.

In regards to the amount of N-acetyl cysteine, normally, changes in result effective variables are not patentable where the difference involved is one of degree, not of kind; experimentation to find workable conditions generally involves the application of no more than routine skill in the art. In re Aller 105 USPQ 233, 235 (CCPA 1955). It would also have been obvious to one of ordinary skill in the art to have adjusted the amount of N-acetyl cysteine in the compositions of the primary reference motivated by the desire to deliver an effective amount of active agent to obtain optimal results, as supported by cited precedent.

In regards to the intended use of the compositions of the combined reference, intended use carries no weight in determining patentability because the compositions of

the combined references are substantially the same as those of the instant claims and therefore should have be able to treat mucositis, because the compositions of the reference and the compositions of the instant claims are substantially the same.

2) Claims 1, 15, 17, 19-20, 24-25, 31, 35, 133-137, 140, 142-143 and 145-152 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoeck et al. (US 6,620,428) in view of Piechota, Jr. (US 5,256,396).

Hoeck et al., the primary reference, is discussed above. The reference differs from the instant claims insofar as it does not disclose the transmucosal delivery compositions comprise poloxamer 407.

Piechota, Jr. discloses topical compositions comprising a vehicle comprising a water-soluble non-ionic block copolymer of ethylene oxide and propylene oxide, the active ingredient to be topically delivered; and water. The preferable copolymer is Poloxamer 407 and is virtually tasteless and odorless and hence has found use in solubilization of aromatics in oral hygiene products such as aqueous alcoholic mouthwashes. The poloxamer compounds are indeed known to be useful in forming gels. Poloxamer 407 is used in concentrations greater than ten percent and less than twenty percent and preferably from twelve to seventeen percent will form aqueous single phase solution is produced which is liquid and flowable at room temperature and will gel in only a few seconds when elevated to about 80.degree. F. The compositions of the reference are broadly applicable to a large number of aqueous compositions intended to deliver active ingredients to a warm animal. A particular useful formulation is

as a mouthwash for delivering therapeutic actives to the oral cavity. Additional components include alcohols such as ethanol, flavors, and humectants. Vehicles such as these are known in the art and there are advantages of using these vehicles[1]. In regards to the viscosity, the vehicles of the reference uses overlapping amounts of poloxamer, 10 to 17%, and water, as the compositions of the instant claims. That being said, the compositions of the reference should have the substantially the same viscosity profile as those of the instant claims. The reference differs from the instant claims insofar as it does not disclose the compositions comprise N-acetyl cysteine.

It would have been obvious to one of ordinary skill in the art to have delivered the compositions poloxamers to deliver the N-acetyl cysteine of the primary reference motivated by the desire to increase drug absorption by the mucous membrane for rapid introduction into the system, as disclosed by the secondary reference.

In regards to the amount of N-acetyl cysteine, normally, changes in result effective variables are not patentable where the difference involved is one of degree, not of kind; experimentation to find workable conditions generally involves the application of no more than routine skill in the art. In re Aller 105 USPQ 233, 235 (CCPA 1955). It would also have been obvious to one of ordinary skill in the art to have adjusted the amount of N-acetyl cysteine in the compositions of the primary reference motivated by the desire to deliver an effective amount of active agent to obtain optimal results, as supported by cited precedent.

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[1] Vehicles such as these are known in the art and there are advantages of using these vehicles. The most commonly reported example of this type of system consists of poloxamer 407 at concentrations ranging from about 10% to 35% by weight of the composition in water. These compositions are administered at

In regards to the intended use of the compositions of the combined reference, intended use carries no weight in determining patentability because the compositions of the combined references are substantially the same as those of the instant claims and therefore should have be able to treat mucositis, because the compositions of the reference and the compositions of the instant claims are substantially the same.

Declaration under 37 CFR 1.132

1) The Declaration by Gary Rosenthal under 37 CFR 1.132 filed July 26, 2007 is sufficient to overcome the rejection of claims 15, 22-23 and 136-141 based upon Krezanoski in view of Boggs and claims 1, 15, 20, 22, 24-25, 35, 38,137, 140 and 142-148 based upon Boggs in view of Stratton.

Previous Rejections

The Declaration reviews the cited prior art and discusses the reasons why one skilled in the art would not combine references such as Krezanoski and Boggs because of the teachings of each references. Although the primary reference teaches a pharmaceutical vehicle similar to that of the vehicles recited in the previous and amended claims, there is no reason why one of ordinary skill in the art would use these vehicles to deliver the N-acetyl cysteine complexes of Boggs. The vehicles of Krezanoski are used to deliver medicinal compounds to the oral mucosa for an increase of drug absorption to the mucosa. Boggs discloses N-acetyl cysteine for delivery of the compound to the teeth and also points out the complexes made with N-acetyl cysteine

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room temperature as liquids. They form a gel upon reaching body temperature. The trigger for

are toxic certain concentrations. Therefore one of ordinary skill would not be motivated to use the vehicles of the primary reference due to toxicity. Theses same concerns apply to the rejection of Boggs in view of Stratton. Therefore in view of the Declaration, the rejections are withdrawn.

New Rejections

The Declaration is insufficient to overcome new rejections Hoeck et al. in view of Krezanoski and Hoeck et al. in view of Piechota, Jr. as set forth in the current Office action. The Declaration discloses why there was not motivation to combine the previously cited references. The newly cited primary reference actually teaches or suggests delivering N-acetyl cysteine transmucosally and discloses using suitable oral vehicles to accomplish this. The secondary references provide a suitable vehicle for transmucosal delivery. Dobroszi et al. disclose these types of vehicles as being commonly used vehicles for delivering active agents (see foot note). The vehicles also comprise the amount of poloxamer recited in the amended claims. Therefore the Declaration is not sufficient to overcome the newly set forth rejections.

2) The Declaration by Antony James Mathews under 37 CFR 1.132 filed July 26, 2007 is sufficient to overcome the rejection of claims 1, 15, 19, 31, 35, 38, 133-137, 142-143 and 146 based upon Dobrozsi et al. and claims 17, 20, 24-25 and 137, 140, 144-145 and 147-148 based upon Dobrozsi et al. in view of Stratton et al.

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converting these compositions to a gel, therefore, is body heat.

Previous Rejections

The Declaration reviews the Dobrozsi reference and gives evidence that most of the compositions of Dobrozsi comprising a poloxamer copolymer are not thermally responsive as formulated. The reference also teaches a different mechanism of gelation and teaches away from compositions that are encompassed by the amended claims. The compositions of the reference comprise the poloxamer copolymer in concentrations of more than 26% poloxamer, which is outside the range recited in the instant claims, which is 5% to 20% poloxamer. The Declaration along with the amended claims makes the instant claims non-obvious over Dobrozsi et al. and Dobrozsi et al. in view of Stratton et al.

New Rejections

The Declaration is insufficient to overcome the new rejections Hoeck et al. in view of Krezanoski and Hoeck et al. in view of Piechota, Jr. as set forth in the current Office action. The Declaration discloses why the compositions of Dobrozsi et al. are different from the instant claims, which include the amount of poloxamer used and the different mechanism of action. The newly cited primary reference teaches or suggests delivering N-acetyl cysteine transmucosally and discloses using suitable oral vehicles to accomplish this. The secondary references provide a suitable vehicle for transmucosal delivery. Dobroszi et al. disclose these types of vehicles as being commonly used vehicles for delivering active agents (see foot note). The vehicles also comprise the amount of poloxamer recited in the amended claims. Therefore the Declaration is not sufficient to overcome the newly set forth rejections.

3) The Declaration by Janice M. Troha was reconsidered in view of the amended claims. The Declaration is discussing intended use of the compositions and is not persuasive to over come the rejections over Krezanoski in view of Boggs or Dobrozsi et al.

Previous Rejections

The Declaration is based on the intended use of the recited compositions and does not show a side-by-side comparison with the compositions of the cited references. This type of argument may have been considered effective if the claims were drawn to a method and not a composition. The Declaration discusses clinical results comparing the vehicles of the instant invention and a water vehicle. It also discloses its efficacy for treating mucositis. It does not show that the compositions of the references don't have the same capabilities or show unexpected results in view of the compositions of the references. In regards to Boggs et al., the Declaration asserts the reference would not lead to an expectation that NAC has efficacy to treat oral mucositis. Mucositis begins in the endothelial layer of the oral mucosa and not at the superficial level of the surface of the gum or tooth, which is the area of interest to Boggs et al. This argument is not persuasive because it does not give reasons as to why one would not use the delivery vehicles of Krezanoski to deliver the compounds of Boggs et al. to the teeth or oral mucosa. In regards to Dobrozsi, it discloses that N-acetyl cysteine (NAC) is used for a different purpose, as a mucolytic/expectorant. The vehicles also require moisture for gelation, which is a different mechanism than disclosed by the instant claims. The

Declaration does not show evidence that the compositions of Dobrozsi do not form gels at higher temperatures or the gels form only from dilution. The Declaration also does not point out that the amount of poloxamer used is different from that of the amended claims.

New Rejections

The Declaration is insufficient to overcome the new rejections Hoeck et al. in view of Krezanoski and Hoeck et al. in view of Piechota, Jr. as set forth in the current Office action. The Declaration discloses N-acetyl cysteine has a different use than what is recited in the instant claims and the mechanism of action. In regards to Boggs et al., it discloses the N-acetyl cysteine is used to treat the teeth and reduce bacteria, not to treat mucositis in the oral mucosa. The newly cited primary reference teaches or suggests delivering N-acetyl cysteine transmucosally and discloses using suitable oral vehicles to accomplish this. The secondary references provide a suitable vehicle for transmucosal delivery. Dobroszi et al. disclose these types of vehicles as being commonly used vehicles for delivering active agents (see foot note). The vehicles also comprise the amount of poloxamer recited in the amended claims. Therefore the Declaration is not sufficient to overcome the newly set forth rejections.

Claims 1, 15, 17, 19-20, 24-25, 31, 35, 38, 133-137, 140, 142-143 and 145-152 are rejected.

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lezah W. Roberts whose telephone number is 571-272-1071. The examiner can normally be reached on 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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